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Nonparametric Dynamical Model of Cardiorespiratory Responses at the Onset and Offset of Treadmill Exercises

--Manuscript Draft--

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Abstract:	This paper applies a nonparametric modelling method with kernel-based regularization to estimate the carbon dioxide production during jogging exercises. The kernel selection and regularization strategies have been discussed; several commonly used kernels are compared regarding the goodness-of-fit, sensitivity and stability. Based on that, the most appropriate kernel is then selected for the construction of the regularization term. Both the onset and offset of the jogging exercises are investigated. We compare the identified nonparametric models, which include both impulse response models and step response models for the two periods, as well as the relationship between oxygen consumption and carbon dioxide production. The result statistically indicates that the steady state gain of the carbon dioxide production in the onset of exercise is bigger than that in the offset while the response time of both onset and offset are similar. Compared with oxygen consumption, the response speed of carbon dioxide production is slightly slower in both onset and offset period while its steady state gains are similar for both periods. The effectiveness of the kernel-based method for the dynamic modelling of cardiorespiratory response to exercise is also well demonstrated.
Response to Reviewers:	We would like to thank the Associate Editor and the Reviewers for their thorough evaluation of our work. The above paper has been revised thoroughly, taking into account all the comments from the Reviewers and the Associate Editor. Responses to Associate Editor:

Your revised manuscript has been reviewed by two of the original referees. One of the reviewers do not find that the original concerns have been satisfactorily addressed during revision, so please make a serious effort to address these concerns as well as to reduce the number of figures (which is very high).

Response: We appreciate the Associate Editor's valuable comments. We revised the paper earnestly according to the Reviewer's comments and reduced the number of figures from 23 to 17.

Responses to Reviewer #2:

1) The authors has addressed my questions properly. I think the manuscript can be accepted.

Response: We appreciate the reviewer for his/her great efforts and supportive feedback.

Responses to Reviewer #3:

1) The purpose of this work is to study the cardiorespiratory response to treadmill exercise. The proposed method includes a nonparametric model associated with a kernel-based regularization. After the selection of the appropriate kernel, the onset and offset responses to exercise were analyzed and compared. The general purpose of the article is interesting and the methodology is nice and appropriate in this context.

Response: We are happy that the reviewer is generally satisfied with our work.

2) However, the paper is a confusing and can't be published without important modifications. Moreover, the main objectives of the paper are not clear. I don't think that the organization of the paper is good. In fact, there are still some results in both method and discussion sections. Moreover, the article contains too much figures (23 figures for the article). The authors should better select the figures and results that are the most significant.

Although the article structure has been revised, the main objectives of the paper are still not clear. There are still some results in the method section. The article is generally long and verbose. The high number of figures (23) induces confusion. Moreover, most of my previous review comments have not been addressed:

Response: Thanks for giving us another chance to modify the paper.
According to the reviewer's comment, we re-organized the structure of the paper. Especially, all the results have been moved to "Results" section, and the most significant figures and results have been selected and included in the revised version based on the reviewer's suggestions.
In summary, we have made the following exchanges in the revised version:
(1)We have moved the results of simulation and kernel selection to the "Results" section (see Subsection 3.1).
(2)We have added the (statistic) analysis part in the "Method" section (see Subsection 2.4).
(3)We moved the comparison figures in the "Discussion" section to "Results" section in Subsection 3.4 and 3.5.
(4)We have reduced the number of figures by deleting figures 7, 8, 16, 21, 22, 23 in the last version.
(5)We have made the pictures close to their relevant explanation by reducing the size.
(6)We have simplified verbose sentences about the physiological background in the "Discussion" section and re-organized the structure "Discussion" section. Please see the red colour marked part of the revised version.
(7)The objects were illustrated in the contribution part in the "Introduction" section and the "Discussion" section.

3) Introduction: The sentence "However, in some cases, the stimulation of the system is insufficient, which is often the case when human is the "system" under investigation as the signals exerting to a human should be well selected to ensure their safety" is difficult to understand. Please rephrase or give a better explanation.

Response: This sentence has been revised as follows:

"However, the signals that exert on a human body should be well selected to ensure the safety. Due to this reason, when the human being is involved in an experiment, the input signals are often limited in both intensity and duration, which leads to insufficient stimulation for the modelling of the system."

4) The authors declare that "The input of the Speed-to-VCO2 system is a step function» Could you better justify this assumption? Have you some information from the treadmill to justify?

Response: To identify a complex dynamic system, such as the response of the human cardio-respiratory system, the pseudo-random binary sequence (PRBS) input is often expected to stimulate the system well. However, for this experiment, as the exerciser must carry a K4b2 gas analyser, if we use a PRBS signal or other complex signals as input, which requires the treadmill changing speed frequently, most subjects will be difficult to follow. And it is also impossible for the treadmill to jump to certain speed instantly. Hence, we apply simple step function as the input signal here.
To do so, we developed an automated treadmill system, which can control treadmill speed in real time to generate a relatively accurate step input signal to the exerciser's cardio-respiratory system.

To identify the dynamic response for both onset and offset exercises, the profiles of the treadmill speed is set as several step functions as shown in Fig. 1. The onset period is from 3 km/h to 8 km/h, and the offset is from 8 km/h to 3 km/h. These two phases can be considered as two steps.

To be clearer, we modify this sentence as "The inputs of the Speed-to-VCO2 system are step functions (i.e., the onset period is from 3 km/h to 8 km/h, and the offset is from 8 km/h to 3 km/h). The exercise protocol of the treadmill speed is illustrated as in Fig. 1.".

5) Section 2.3: "A is the steady state gain and B is the time constant": Why don't you used the usual notation for a gain and a time constant K and T? You should provide the units for the gain and the time constant.

Response:

We appreciate the reviewer's valuable suggestion. We have changed the symbols of the steady state gain and time constant accordingly, i.e., "A and B" have been changed as "K and T".

It should be noted that the character "K" was used as the symbol of kernels in the previous version. To avoid confusion, in the revised version, we used "P" to represent the kernel function.

During simulation, we treat both K and T as constants without units. In experiments, the unit for K is [(ml/min/kg)/(km/hour)] and the unit for T is [second].

6) The authors give values for the kernel parameters. The choice of these values should be better justify and the units of each parameter should be added. Moreover, the authors should discuss their influence of the results.

Response: We tune the parameter partially according to the suggestions from [16] as follows:
•For the ''DI'' kernel, further assume that $0.7 \le \lambda < 1$.
•For the ''DC'' kernel, further assume that $0.72 \le \lambda < 1$ and $-0.99 \le \rho \le 0.99$.
•For the ''SS'' kernel, further assume that $0.9 \le \lambda < 1$ (λ is as the same as β in our paper).

Finally, we selected the best parameters based on the simulation results (e.g., we choose ρ=0.999 for DC kernel). The kernel parameters are constants without units.

The influence of the parameters is shown in Fig. 4. This figure presents the identified Impulse Responses with different kernel parameters. It also shows the parameter sensitivity of each kernel. Based on that, the Stable Spline kernel is selected due to its goodness-of-fit and less sensitivity with parameters. Please see Fig. 4 in the revised version for details.

[16] Tianshi Chen and Lennart Ljung. Implementation of algorithms for tuning parameters in regularized least squares problems in system identification. Automatica, 49(7):2213–2220, 2013.

7) Concerning the goodness-of-fit of the estimated output, you should clearly explain how it is calculated and give the units. Moreover, the SS kernel was chosen but you should precise if there are significant differences between the fit associated with each kernel (see fig. 6)?

Response: The goodness-of-fit of the estimated output is calculated by fit ratio NRMSE (normalised root mean square error) and the details are given in Equation (12). The unit of the fit ratio is 1. Also, in the revised version, we updated the average fitness and box-plot according to the latest simulation results.

To show the significance, we add the following part in Page 6-7 to illustrate the significant differences of the goodness-of-fit of the kernels:
"Thus, we applied T-test to verify the significant difference of the goodness-of-fit. All the results show that $p < 0.0001$ which indicate they are of significant difference. That means the influence of different kernels on the results is significant."

8) I believe that this section contains results. The authors should better separate methods and results. Method section should only include a description of evaluation methodology and not all results.

Response: We agree with the reviewer. Accordingly, we move the results of simulation and kernel selection to the "Results" section in Subsection 3.1.

9) Section 2.2: Have you included men and women in your study? Have you find any gender differences in the cardiorespiratory response to exercise?

Response: All the subjects are male in to minimize the gender influence on the results. To avoid ambiguity, we added "male" in the sentence on Page 5 as follows:
"20 untrained healthy male subjects were asked to run on the treadmill."

10) Fig. 2/Fig. 3: I don't understand how you obtained these simulated signals? You should better describe the model used to obtained these simulated signals.

Response: The description of the simulated signals about Fig.2 has been given in Subsection 2.2 Kernel Selection in Page 5:

"A step function is selected as the input , and the simulated output is polluted by a Gaussian white noise with 1 Signal-Noise Ratio (SNR). The sampling time is selected as second. The input and output of the simulated system are shown in Fig. 2"

The description of Fig.3 has been given in Subsection 3.1 in Page 6:

"At first, we use the LS method without kernel technique to perform the identification. The identified impulse response (IR) of the system is shown in Fig. 3."

We also modified the position of figures in this section to make them clearer.

11) Section 3.1: "In this part, we selected the data from t1 = 500s to t2 = 900s": Why not from t1 = 500s to t2 = 900s? Equation 12: Maybe, you should only precise that

N=400?

Response: Apologies for the typos. We revised the manuscript accordingly with details as follows.

In Page 7, at the beginning of Subsection 3.2: “In this part, we selected the data from to (see Fig. 1) for the modelling of onset impulse response.”.

In Page 8, at the beginning of Subsection 3.3: “We select the data from =901s to =1300s for the modelling of offset period.”.

Also, in the revised version, we modified the limits in Equation (13) from 0-399 to 1-400.

12) Fig. 7: How did you obtain this signal? It is an acquisition or an estimation?

Response: Fig. 7 in the previous version is the protocol of speed signal. This protocol can be accurately implemented by using the developed automated treadmill system, i.e., we can control the treadmill speed to follow the profile in real time. Although this signal has appeared in Fig. 1 together with the measured VCO2, in the previous version, to emphasize this exercise protocol, it is separately provided in Fig. 7.

In the revised version, to save space, we delete this figure.

13) Fig. 8: In my opinion, figure 8 does not bring any information.

Response: We agree with the reviewer. To save space, in the revised version, we also delete this figure since this typical experimental scenario is imaginable.

14) Fig. 9/ Fig. 10/ Fig. 11/ Fig. 12: I don’t understand if the model was fitted for each subject or for a mean subject. Do these curves correspond to average estimations for all subjects? Please provide a more precise description of the method used to obtain these curves.

Response: The dotted lines in these figures represent the identified impulse response model by using each participant’s measurement data and the bold line stands for the identified impulse response model by using the averaged value of the 20 participants.

Accordingly, we modified the explanation in Subsection 3.2 and 3.3 to clarify what the dotted lines and the bold line represent.

15) Generally, I’m not convinced that a first order model is not appropriate because the dynamic of the response seem very closed to a RC charging curve. You should absolutely justify this point.

Response: Most previous studies applied parametric modelling approaches for the estimation of cardiorespiratory response to exercise. However, the complexity of the parametric model is bounded even if the amount of data is unbounded. This makes them not very flexible.

In this paper, we applied a nonparametric model (impulse response model) based identification method for VCO2 and VO2 modelling. Unlike the estimation of a parametric model (e.g., transfer function), the estimation of impulse response does not need to consider the order of the system. The major advantage of using a nonparametric modelling approach is its flexibility. That is, the amount of information that the nonparametric model can capture as the amount of data grows.

On the other hand, as the human cardiorespiratory system is complex, the dynamics of running speed to VO2 consumption during exercise might have different characteristics for each individual exerciser. To describe this dynamic system, researchers proposed several different models already. The first order system is one of the most commonly used models, but not the only one. It is quite hard to identify the exact order when the input is a single step signal and the observation is with large noise. The step response of a second or higher order system could look like a first-order system if the high order system can be factorized as several first order subsystems. As non-parametric modelling approach does not need to identify the order of the system explicitly, its advantage is obvious.

Also, in previous dynamic modelling, the stimulation of system is often limited, and the previous method cannot correctly estimate a high-order system without enough stimulation, especially for the identification of impulse response. Therefore, for most researches, the system was approximated as first order. However, due to the individual difference, it is likely that some people are quite different from others.

Hence, instead of spending lots of effort on exploring the structure of the system, we proposed this nonparametric modelling method to provide a more accurate estimation.

16) Section 4: The discussion includes some parts that should included in the method section (description of the statistical analysis…) and others parts that should be placed in the results (especially all figures).

Response: We appreciate the valuable advice. Some parts of discussions including the description of the statistical analysis in the discussion section have been moved to the "Method" section (see Subsection 2.4 in the revised version). Also, we have moved the comparison figures in the "Discussion" section to the "Results" section (see Subsections 3.4 and 3.5 in the revised version).

17) "In other words, the results of our study show that for the same speed change, human body exhales out more CO2 in onset than offset." Could you provide an accurate physiological explanation?

Response: In the revised version, we have illustrated this claim in the "Discussion" section (see Subsection 4.1) and added a sentence after this claim to refer the readers to the physiological explanation in the "Discussion" section:

"As we observed, for the same speed change, the carbon dioxide consumption in onset is more than offset. The reason behind this observation is the fact that ATP is the "molecular currency" for intracellular energy transfer, storage as well as transfer chemistry energy. With the increasing of the exercise intensity, the human body has to consume more ATP in onset period than that of in offset period. Human body provides ATP and produces carbon dioxide by respiration. Thus, the participants produce more carbon dioxide in onset period than offset for the same speed changing rate. This observation is also related to the "oxygen debt" [4][32][34], which is first proposed by Hill [3]. The "debt" occurs during the onset period because the stored credits are expended.

[3] Archibald V Hill, CNH Long, and H Lupton. Muscular exercise, lactic acid, and the supply and utilisation of oxygen. Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character, 97(681):84--138, 1924.
[4] Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J appl Physiol, 35(82):236, 1973.
[32] Yi Zhang, Azzam Haddad, Steven W Su, Branko G Celler, Aaron J Coutts, Rob Duffield, Cheyne E Donges, and Hung T Nguyen. An equivalent circuit model for onset and offset exercise response. Biomedical engineering online, 13(1):145, 2014.
[34]. Nicholas M Beltz, Fabiano T Amorim, Ann L Gibson, Jeffrey M Janot, Len Kravitz, Christine M Mermier, Nathan Cole, Terence A Moriarty, Tony P Nunez, Sam Trigg, et al. Hemodynamic and metabolic responses to self-paced and ramp-graded exercise testing protocols. Applied Physiology, Nutrition, and Metabolism, (999):1–8, 2018.

18) Fig. 14: I don't see the interest of the figure? Please explain.

Response: In the previous version, Fig. 14 showed the normalized and averaged estimation of VdCO2 for both onset and offset periods to compare the difference between the two periods. The corresponding explanation has been presented in the first paragraph of Subsection 3.4 in Page 8. We also re-arranged the position of the picture to make it clear.

“To see this difference in the response speed, we normalized the averaged estimation of VdCO2 in onset and offset period, which is shown in Fig. 11.”

19) Fig. 16/ Fig. 21: I don’t know if these figures are necessary. Maybe, you should only provide the statistical analysis.

Response: In the previous version, these two figures together with Fig. 22 illustrated whether the Gain and Time index follow the normal distribution or not. We choose Paired T-test if it follows and chooses Rank Sum test if not. However, to save space, we have deleted Fig. 16, 21, 22 and provided the statistical analysis by words and tables (see Subsection 3.4 and Table 2-4).

20) “Moreover, we calculate the correlation coefficient between the estimated VdCO2 and VdO2”. Why do you choose to calculate the correlation coefficient here? The objectives of the paper are not clear at all.

Response: Apart from the similarity of the dynamic responses indicated in the identified impulse response models, we calculate the correlation coefficient between the estimated VdCO2 and VdO2 to investigate the correlation relationship between them. It may be helpful if they are highly correlated to some extent. For example, for the gas collection during the experiment, it is often the case that the assessment of the exhaled gas components (with more carbon dioxide) is simpler than that of the inhaled gas (with more oxygen), i.e., the measurement of carbon dioxide production is more convenient than that of oxygen consumption. Then, if it is necessary, the measurement of VdO2 can be bypassed, but estimated by using VdCO2 instead to reduce the cost.

21) Section 4.3: The physiological explanation should be based on precise and recent references to justify all assumptions. Generally the discussion section is very confusing.

Response: We have comprehensively re-organized the structure of the “Discussion” section and interpreted the results with the physiological explanations. The literature we referred are the original literature with the similar physiological explanation that may be a long time ago but well cited in the society. In the revised version, we add some recent references, which has cited these papers and closely related to the explanations (e.g., [26] [28] [32]).

“In this section, we attempt to explain the results from a physiological point of view. The explanation about the similarity and difference between onset vs. offset and VdCO2 vs. VdO2 are illustrated respectively in Subsection 4.1 and 4.2.

Aerobic respiration produces carbon dioxide and water, resulting in the releasing of energy and generating large amounts of Adenosine Triphosphate (ATP, also known as adenine nucleoside triphosphate). ATP transports chemical energy within cells for metabolism. Under normal circumstances, only considering the case of glucose for energy, in aerobic breathing, the product is carbon dioxide and water. The total reaction of aerobic respiration is shown in Eq.(14). The concept of Respiratory Quotient [31] (referred as RQ or R, the VCO2 divided by VO2 in local tissue) was presented, which is equal to when glucose is the only available source for energy according to Eq.(14). Every 1 litre of oxygen will produce 1 litre of carbon dioxide, and the volume ratio of carbon dioxide and oxygen is 1[29][30].

Based on the above background about aerobic respiration, the results and their physiological explanations are summarized as follows.

4.1 Comparison between Onset and Offset Period of VdCO2

• The Time Index of VdCO2 in onset is similar to offset and the gain of VdCO2 in onset is bigger than offset.

As we observed, for the same speed change, the carbon dioxide consumption in onset is more than offset. The reason behind this observation is the fact that ATP is the "molecular currency" for intracellular energy transfer, storage as well as transfer chemistry energy. With the increasing of the exercise intensity, the human body has to consume more ATP in onset period than that of in offset period. Human body provides ATP and produces carbon dioxide by respiration. Thus, the participants produce more carbon dioxide in onset period than offset for the same speed changing rate. This observation is also related to the "oxygen debt" [4] [32][34], which is first proposed by Hill [3]. The "debt" occurs during the onset period because the stored credits are expended.

4.2 Comparison of VdCO2 and VdO2

• Similarity: The VdCO2 and VdO2 are significantly related and the gains of VdCO2 and VdO2 are similar in both periods.

The similar gain and correlation coefficient of VdCO2 and VdO2 also work in concert with the respiration formula as Eq. (14).

• Difference: The Time Index of VdCO2 is bigger than that of VdO2 in both periods so the VdO2 shows a quicker response speed.

The different Time Index means a different gas delivery rate. The Fig. 3 in Williams's research [33] shows the same result. For their half-time constant, oxygen consumption is smaller than carbon dioxide elimination. This is also related to the O2 debt and excess CO2 and respond to the Subsection 4.1. The Fig. 2 of Karlman's research [4] also shows that the R is over 1 which is same to our results and explain it by a buffer system. ”

[3] Archibald V Hill, CNH Long, and H Lupton. Muscular exercise, lactic acid, and the supply and utilisation of oxygen. Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character, 97(681):84--138, 1924.
[4] Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J appl Physiol, 35(82):236, 1973.
[26] Jerzy A Zoladz, Bruno Grassi, Joanna Majerczak, Zbigniew Szkutnik, Michal Korosty ski, Marcin Grandys, Wieslawa Jarmuszkiewicz, and Bernard Korzeniewski. Mechanisms responsible for the acceleration of pulmonary vo2 on-kinetics in humans after prolonged endurance training. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 307(9):R1101--R1114, 2014.
[28] Kenneth J Hunt, Simon E Fankhauser, and Jittima Saengsuwan. Identification of heart rate dynamics during moderate-to-vigorous treadmill exercise. Biomedical engineering online, 14(1):117, 2015.
[31] François Peronnet, Denis Massicotte, et al. Table of nonprotein respiratory quotient: an update. Can J Sport Sci, 16(1):23--29, 1991.
[32] Yi Zhang, Azzam Haddad, Steven W Su, Branko G Celler, Aaron J Coutts, Rob Duffield, Cheyne E Donges, and Hung T Nguyen. An equivalent circuit model for onset and offset exercise response. Biomedical engineering online, 13(1):145, 2014.
[33] William E Berg. Individual differences in respiratory gas exchange during recovery from moderate exercise. American Journal of Physiology--Legacy Content, 149(3):597--610, 1947.
[34]. Nicholas M Beltz, Fabiano T Amorim, Ann L Gibson, Jeffrey M Janot, Len Kravitz, Christine M Mermier, Nathan Cole, Terence A Moriarty, Tony P Nunez, Sam Trigg, et al. Hemodynamic and metabolic responses to self-paced and ramp-graded exercise testing protocols. Applied Physiology, Nutrition, and Metabolism, (999):1–8, 2018.

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Abstract This paper applies a nonparametric modelling method with kernel-based regularization to estimate the carbon dioxide production during jogging exercises. The kernel selection and regularization strategies have been discussed; several commonly used kernels are compared regarding the goodness-of-fit, sensitivity and stability. Based on that, the most appropriate kernel is then selected for the construction of the regularization term. Both the onset and offset of the jogging exercises are investigated. We compare the identified nonparametric models, which include both impulse response models and step response models for the two periods, as well as the relationship between oxygen consumption and carbon dioxide production. The result statistically indicates that the steady state gain of the carbon dioxide production in the onset of exercise is bigger than that in the offset while the response time of both onset and offset are similar. Compared with oxygen consumption, the response speed of carbon dioxide production is slightly slower in both onset and offset period while its steady state gains are similar for both periods. The effectiveness of the kernel-based method for the dynamic modelling of cardiorespiratory response to exercise is also well demonstrated.

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Keywords Nonparametric modelling · Cardiorespiratory response to exercise · Treadmill exercise · Carbon dioxide production

1 Introduction

Decades ago, some sports physiology laboratories had used the Douglas bag and the Scholander gas analyzer [1] to measure the oxygen (O_2) uptake and the amount of carbon dioxide (CO_2) produced before, during, and after exercise. Over the last dozens of years, automated portable gas analysis systems had been developed and applied in various sports fields for energy consumption assessment [2]. The study of oxygen uptake was both the traditional theme of sports physiology study and one of the mainstreams of current and future sports physiology research. The characterization of gas exchanging attracted a lot of scholars to work in the field. Hill et al. [3] studied oxygen consumption (VO_2) and investigated its recovery curve. After moderate exercise, it is a logarithmic equation, which is equally applicable to the recovery curves of carbon dioxide production (VCO_2). Similarly, William and Berg illustrated the equation of carbon dioxide elimination is equal to oxygen consumption. Researches about the VO_2 and VCO_2 during the exercise also had been developed.

Modelling method is widely used in the biological signal analysis [5][6][7]. Several research studies for the modelling of the dynamics of physiological signal in response to treadmill exercise were also conducted [8][9][10]. To the best of our knowledge, all the existing studies only utilized classical system identification approaches, e.g. the Least Square (LS), Maximum Likelihood (ML) and Prediction Error Method (PEM). However, the signals that exert on a human body should be well selected to ensure the safety. Due to this reason, when the human being is involved in an experiment, the input signals are often limited in both intensity and duration, which leads to insufficient stimulation for the modelling of the system. In this case, the LS/ML/PEM equipped with classical model structure selection approaches often fail to obtain an appropriate model with desired accuracy and robustness for cardiorespiratory response estimation, which is based on insignificantly stimulated short recording data polluted by artifacts and noise [11][12][13].

The recently developed system identification approaches are not only based on plenty of physical experimental data but also emphasizing more on prior knowledge of the system under estimation. System prior information is often applied to model complexity selection, which is the most critical step for system modelling. In some papers [14][15], system dynamics is depicted by nonparametric models rather than the most commonly used first/second order linear time-invariant models. Often, nonparametric methods are used when the prior information is insufficient to determine a parametric model structure. The new approach [13][17] which well utilizes the prior information is based on the kernel-based regularization approach. By using kernel technique, prior information is adopted in the identification process by assigning an appropriate kernel to the index function. Specifically, papers [15] [18][19] [20] introduced the regularization terms and the kernel designing strategies for nonparametric system identification. Based on authors' experiences, for the investigation of the dynamics of cardiorespiratory response to exercise, the new kernel-based nonparametric approach should be the best option to greatly improve the robustness and accuracy.

The treadmill exercise is similar to human's daily life running or walking status so it could be applied to analyze the mechanism of one's exercise. It is well documented that regular treadmill exercise can greatly improve the human cardiovascular system, e.g., increase total oxygen demand and consumption (the amount of increase depending on the size of the muscles used), and VO_2 Max. Besides, the treadmill is a good choice for exercise modelling because the model needs an accurate input to ensure a steady workload and exclude other effect factors. Some research [28] applied Heart Rate (HR) to make the analysis, but it can easily be affected by human's motion or other aspects. In this way, other researchers choose how the gas changes during the exercise as an index. Among the studies of cardiorespiratory response to exercise, researchers preferred to choose oxygen consumption as the index. Both linear and nonlinear static models [22][23][24] had been proposed based on the walking speed. Furthermore, some researchers modelled the VO_2 response with a monoexponential curve [25][26][27]. In these studies, the oxygen production could indicate the respiratory gas exchange, energy providing situation, the energy saving phenomenon, the differential effect of training tense and other biological phenomenon. Some of the researchers had also recorded the VCO_2 as an auxiliary data for analysis.

The above studies present different aspects of Kinematics and the pattern of gas exchange. However, VCO_2 is uncommonly applied. What's more, the dynamic changing of the VCO_2 and VO_2 during the different periods of exercise and their relationship need a deeper investigation to get a comprehensive understand for human's exercise mechanism. In this paper, we apply the nonparametric modelling method [13][17] to identify the relationship between VCO_2 and the speed of the treadmill. The inputs of the $Speed-to-the-VCO_2$ system are step functions (i.e., the onset period is from $3km/h$ to $8km/h$, and the offset is from $8km/h$ to $3km/h$). The exercise protocol of the treadmill speed is illustrated as in Fig. 1. We adopted the kernel-based estimation method for this modelling. The data were collected from 20 untrained participants in the treadmill exercise. After the identification, we make a statistical comparison between the onset period (from walking to running) of the speed and the offset period (from running to walking). Besides, we analysed the relationship between the VO_2 and the VCO_2. The contributions of the paper are listed as follows:

- The kernel-based nonparametric modelling approach has been applied to describe the dynamics of both VO_2 and VCO_2 responses to exercise.
- Based on comprehensively comparative numerical analyses, the SS kernel has been selected as the best kernel for the identification of dynamic response to exercise regarding the goodness-of-fit and parameter insensitivity.
- Based on the reliable experimental data acquired from twenty subjects, the dynamic models of the VO_2 and VCO_2 for exercise responses for both onset and offset of exercise have been identified.
- Comprehensively statistical analyses are performed to compare the dynamic characteristics of the onset and offset exercise responses for VO_2 and VCO_2, and several useful conclusions have been made to provide instructive guidance for the regulation of exercise intensity.

The remainder of this paper is organized as follow. The methods including regularization, kernel selection, experiment and analysis are presented in Section 2. The simulation, kernel selection, identification results and comparisons are shown in Section 3. The analysis of the results and physiological explanation are discussed in Section 4. Finally, conclusions are drawn in Section 5.

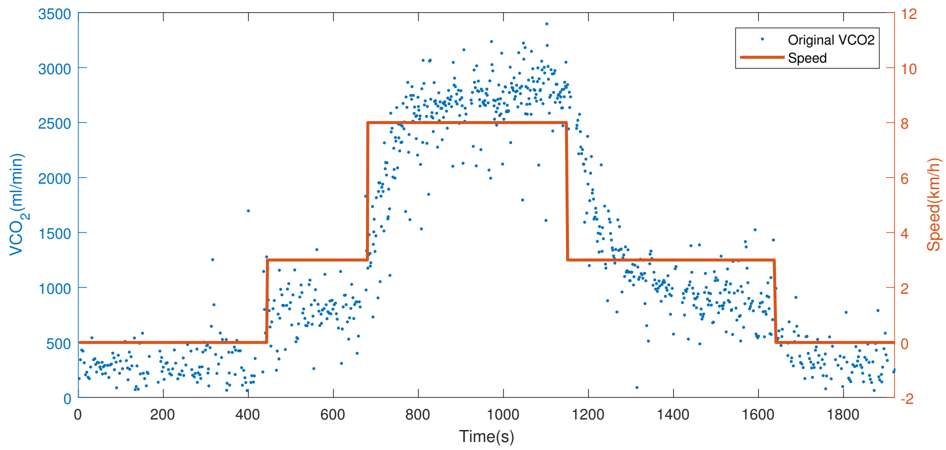

Fig. 1 Raw VCO_2 and treadmill speed during the exercise.

2 Methods

According to previous studies, for the VO_2 during exercise, the exponential function was applied to describe the dynamic performance [25][26][27]. Puente [25] demonstrated that the VCO_2 could also be described by the same as:

$$VCO_2(t) = VCO_2^0 + R_A[1 - e^{-(t-T_D)/\tau}]. \tag{1}$$

where $VCO_2(t)$ is the CO_2 production at time t, VCO_2^0 is the initial value of CO_2 production, R_A is the response amplitude, T_D is the time delay, and τ is the time constant.

This function implies that Puente treated the model of VO_2 response as a first-order dynamic system with constant time delay. However, for different individuals, the patterns of VCO_2 responses to exercise are quite different based on our observations. Hence, the first order model would not be a good choice to use. In this study, as discussed in the introduction section, we will adopt the nonparametric kernel-based modelling method to obtain a better result. Specifically, as one of the most commonly used nonparametric model, the finite impulse response (FIR), will be used to describe the characteristics of the system.

We first introduce the kernel-based estimation method in section 2.1 and then present the kernels we intend to select in section 2.2. The details of the experiment are presented in section 2.3 and the statistical methods are shown in section 2.4.

2.1 Kernel Based Estimation Method for the Modelling of Finite Impulse Response

The data of carbon dioxide production and the speed of the treadmill are shown in Fig. 1, which indicates the step response of VCO_2 regarding treadmill speed.

As previously mentioned, we will use nonparametric estimation based on kernel technique to build the VCO_2 model for treadmill exercise. The relationship between the speed of the treadmill and the VCO_2 can be considered as a single input single output (SISO) system. We consider the discrete case and assume the sampling time is t. Thus, the discrete time output calculated by impulse response can be expressed as (2):

$$y(t) = \sum_{\tau=0}^{\infty} u(t-\tau)g[\tau] + \varepsilon(t),\ t = 1,2,\ldots,N, \tag{2}$$

where $u(t)$ is the input, $y(t)$ is the output, $g(\tau)$ is the impulse response, $\varepsilon(t)$ is Gaussian white noise, and N is the total number of sampling.

The model output (predictor) is defined as:

$$P_t[g] = \sum_{\tau=0}^{\infty} u(t-\tau)g[\tau]. \tag{3}$$

Then the cost function regarding estimation error can be written as:

$$\hat{y}(t) = \sum_{t=1}^{N} (y(t) - P_t[g])^2. \tag{4}$$

In order to rewrite (2) in a vector form, we stack all the elements (row) in $y(t)$ and $u(t-\tau)$ to form the matrices $\boldsymbol{Y}$ and $\boldsymbol{\phi}$. Then the minimum value of the cost function can be solved by LS estimation or ML estimation. We define $g(\tau) = \boldsymbol{\theta} \in \mathbb{R}^m$, where the vector $\boldsymbol{\theta} \in \mathbb{R}^m$ contains the FIR coefficients. Then the LS estimation of the parameters $g(\tau)$ is:

$$\hat{\boldsymbol{\theta}} = \arg\min_{\boldsymbol{\theta}\in\mathbb{R}^m} \|\boldsymbol{Y} - \boldsymbol{\phi}\boldsymbol{\theta}\|^2. \tag{5}$$

However, the measurements of VCO_2 from gas analyzer contain various artifacts and are polluted by various noises. To regularize the estimation, a regularization term can be added to (5). Regularization approaches aim to put "soft" constraints on the structure $\boldsymbol{\theta}$ [18][19]. We define $J_R(\boldsymbol{\theta})$ as the regularization term, and it belongs to a Reproducing Kernel Hilbert Space (RKHS) $\mathscr{H}$. If we only consider FIR, the norm $\|g_{\boldsymbol{\theta}}\|_{\mathscr{H}}$ in the space $\mathscr{H}$ can be expressed via a quadratic form in (6), where $\boldsymbol{P}$ is a suitable kernel matrix:

$$J_R(\boldsymbol{\theta}) = \boldsymbol{\theta}^{\mathrm{T}}\boldsymbol{P}^{-1}\boldsymbol{\theta}. \tag{6}$$

The structure of $\boldsymbol{P}$ can account for different properties associated with prior information, which will be discussed in next subsection. The estimation of $\boldsymbol{\theta}$ can then be expressed as follow:

$$\begin{aligned}\hat{\boldsymbol{\theta}} &= \arg\min_{\boldsymbol{\theta}\in\mathbb{R}^m}\left(\|\boldsymbol{Y}-\boldsymbol{\phi}\boldsymbol{\theta}\|^2+\gamma\boldsymbol{\theta}^{\mathrm{T}}\boldsymbol{P}^{-1}\boldsymbol{\theta}\right)\\ &= \left(\boldsymbol{P}\boldsymbol{\phi}^{\mathrm{T}}\boldsymbol{\phi}+\gamma I_m\right)^{-1}\boldsymbol{P}\boldsymbol{\phi}^{\mathrm{T}}\boldsymbol{Y},\end{aligned} \tag{7}$$

where γ is a positive scalar, and $I_m \in \mathbb{R}^{m\times m}$ is an identity matrix with the dimension of $m \times m$.

2.2 Kernel Selection

The construction of kernel $\boldsymbol{P}$ is made up of two parts: the kernel structure design and hyper-parameter estimation. Many researchers have strived for kernel design [11][12][13][17][21]. Among them, the Stable Spline (SS) kernel, the Diagonal/ Correlated (DC) kernel, and the Diagonal (DI) kernel have been well developed. Therefore, we select the following kernels for simulation study to achieve a better estimation of the impulse response of VCO_2.

- SS kernel:

$$P(i,j) = \frac{c}{2}e^{-\beta min(i,j)} - \frac{c}{6}e^{-3\beta max(i,j)}, \tag{8}$$

  where $c \geq 0$, $0 \leq \beta < 1$.
- DC kernel:

$$P(i,j) = c\lambda^{\frac{i+j}{2}}\rho^{|i-j|}, \tag{9}$$

  where $c \geq 0$, $0 \leq \lambda < 1$, $\rho \leq 1$.
- DI kernel:

$$P(i,j) = \begin{cases} c\lambda^i, \text{ if } & i = j \\ 0, \text{ else} & \end{cases} \tag{10}$$

  where $c \geq 0$, $0 \leq \lambda < 1$.

According to (1), the relationship between the CO_2 production and the treadmill speed can be approximately considered as a first order system. For this reason, we start the simulation study by using a first order system with different parameter settings. The detailed settings of the system are as follows:

$$Y(s) = \frac{K}{Ts+1}U(s), \tag{11}$$

where K is the steady state gain and follows the uniform distribution U(5, 15). T is the time constant and follows U(15, 25).

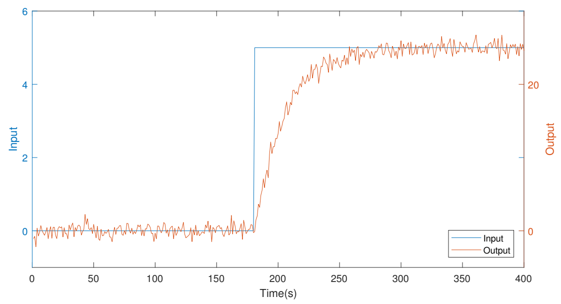

Fig. 2 An input and output pair of the simulated system.

A step function is selected as the input $u(t)$, and the simulated output $y(t)$ is polluted by a Gaussian white noise with 1 dB Signal-Noise Ratio (SNR). The sampling time is selected as 1 second. The input $u(t)$ and output $y(t)$ of the simulated system are shown in Fig. 2.

2.3 Experiment

20 untrained healthy male subjects were asked to run on the treadmill. During the exercise, all data including VCO_2 and VO_2 are collected by a portable gas analyser-K4B2. The UTS Human Research Ethics Committee (UTS HREC 2009000227) had approved this experiment and the informed consent from all participants before the commencement of data collection was obtained. The statistical physical information of the participants is shown in Table 1.

Table 1 Information about the subjects

Information	Age($year$)	Height(cm)	Weight(kg)
Mean	46.4	176.6	91.2
Standard Deviation	5.68	4.40	11.37

Before the experiment, the subjects were asked to sit for five minutes and then stand for two minutes. The physical conditions and the environment settings were standardised for all participants. During the exercise, the participants first were walking at 3 km/h for four minutes and then running at 8 km/h for eight minutes followed by walking at 3 km/h for eight minutes before stopping. To exclude the impact of the subjects' weight on VCO_2 and VO_2, the VCO_2 and VO_2 were both divided by the weight (Kg) of each subject. The normalized VCO_2 and VO_2 are recorded as V_dCO_2 and V_dO_2.

2.4 Statistic

- The term "Time Index" as a reflection of response speed is introduced, which indicates the time when the output reaches the 75% of maximum.
- The *histogram* and *normal probability* are plotted in Matlab to present whether the gain and Time Index follow a normal distribution or not. *Paired* T-test is used for the one which follows and *Rank Sum* test is used for the one which does not follow. Generally, $P < 0.05$ was considered as statistically significant. Where $h = 0$ means we cannot determine the size of the two sets of data by mean value because the distinction is small. Meanwhile, the mean value can be used to make the comparison when $h = 1$ because the distinction is significant.
- The *correlation coefficient* between the estimated V_dCO_2 and V_dO_2 is calculated in order to know about the correlation between them. Normally, if the correlation coefficient is between ± 0.80 to ± 1.00, the two variables are highly correlated.
- We calculated the difference of Time Index (V_dCO_2 minus V_dO_2) in two periods to show whether it is all positive or not.

3 Results

In this section, we first present the simulation and kernel selection result in section 3.1. Then the modelling result for the onset and offset period is represented respectively in section 3.2 and 3.3. The IR and estimated V_dCO_2 of both periods are also shown. Furthermore, we develop the comparison of onset vs offset and V_dCO_2 vs V_dO_2 from the aspect of the impulse response, step response and estimated output in section 3.4 and 3.5. Different statistic methods are employed for the analysis.

3.1 Simulation and kernel selection

At first, we use the LS method without kernel technique to perform the identification. The identified impulse response (IR) of the system is shown in Fig. 3. We can observe that

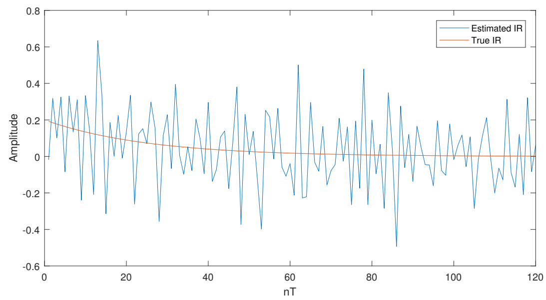

Fig. 3 The estimated IR by using the classical LS estimation.

the estimation error is big in the sense that the noise is amplified. Next, we will show the effectiveness of the kernel-based regularization method. Then, we try to select the best parameters for each kernel and compare the sensitivity to parameters of the three kernels. The results are shown in Fig. 4.

After that, we tune the parameters partially according to the constraints introduced in [16] and make the final choice by the best results in our simulation. The selected optimal parameters of the kernels and the regularizer are listed below [11][12][13][17][21].

- SS kernel: $c = 1, \beta = 0.987$.
- DC kernel: $c = 0.3, \lambda = 0.999, \rho = 0.999$.
- DI kernel: $c = 0.3, \lambda = 0.95$.
- Regularizer: $\gamma = 4$.

We make a comparison between the true IR and the estimated IR based on the above-listed kernels. As we can see, the IR from SS kernel is closer to the true value compared to the others. At the same time, we compare the estimated output and the true output. We carry out the simulation for 20 times. One of the simulation results about IR and estimation is shown in Fig. 5.

The goodness-of-fit of the estimated output is calculated by the fit ratio NRMSE (normalised root mean square error) which is defined as:

$$\text{Fit Ratio} = \left(1 - \frac{||\hat{Y}_N - Y_N||}{||Y_N - \text{mean}(Y_N)||}\right). \tag{12}$$

The averaged results are shown as follows and the simulation result is shown in Fig. 6.

- SS kernel: Average fit=0.9395.
- DC kernel: Average fit=0.9439.
- DI kernel: Average fit=0.9547.

Regarding the goodness-of-fit, the kernel-based methods outperformed the classical LS estimation. The three kernels have a similar fitness because the mean value of their fitness are between 0.93-0.96. Thus, we applied T-test to verify the significant difference of the goodness-of-fit. All the results

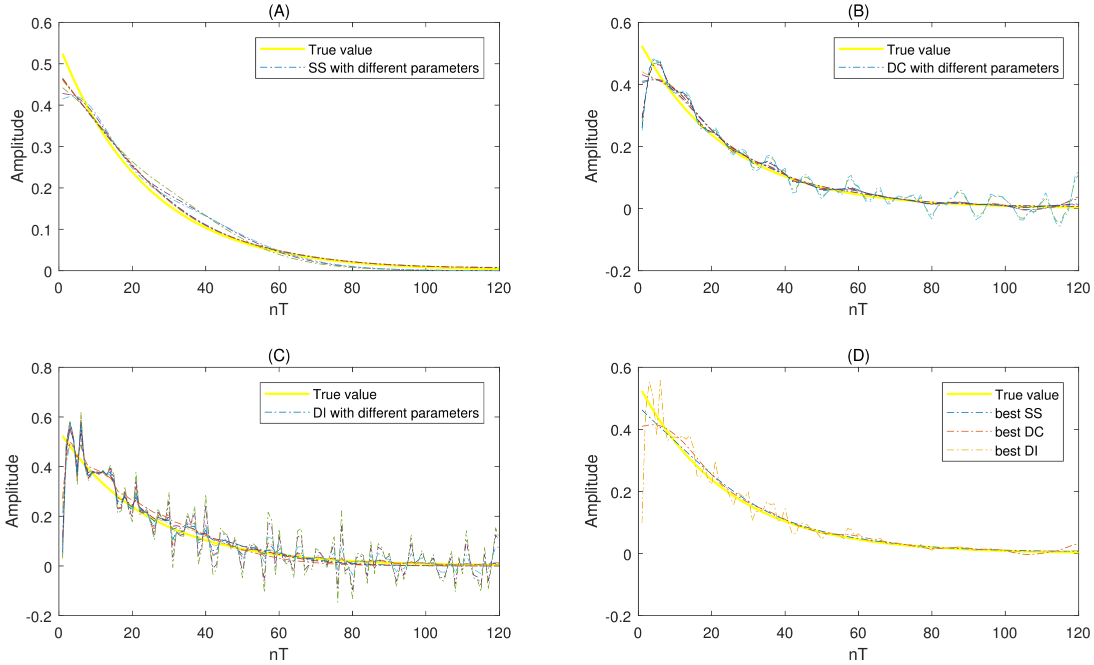

Fig. 4 Comparison results of the kernel with different parameters: (A) SS kernel with different parameters. (B) DC kernel with different parameters. (C) DI kernel with different parameters. (D) The comparison of the three kernels with well selected parameters and true IR.

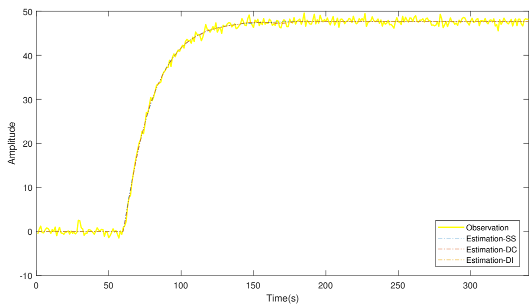

Fig. 5 Observation and estimation of three types kernels.

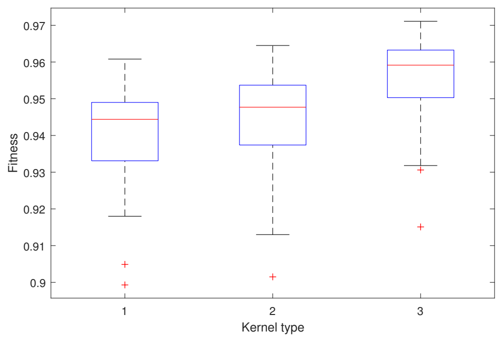

Fig. 6 Box plots of the estimations by using the SS, DC, DI kernels [from left to right].

show that $p < 0.0001$ which indicate they are of significant difference. That means the influence of different kernels on the results is significant. We could observe from the IR in Fig. 4 that the DI and DC kernel is over-fitted although they have a higher fitness. Moreover, the SS kernel has a more smooth IR and less sensitivity to the parameter. Thus, we choose the SS kernel to get a better IR estimation.

3.2 Modelling of Onset Period

In this part, we selected the data from $t_1 = 501s$ to $t_2 = 900s$ (see Fig. 1) for the modelling of onset impulse response. The sampling rate of the V_dCO_2 is irregular since the gas response recorded by K4B2 is breath by breath based. Thus, the raw data of V_dCO_2 and V_dO_2 have been interpolated and filtered by a median filter. For the recorded 400 observations, to remove the offset, the average value of the onset period for the initial 150 data is deducted. The order of the impulse response model is selected as 400.

The IR model can be expressed as:

$$y[n] = g[1]u[n-1] + g[2]u[n-2] + \ldots + g[400]u[n-400]$$
$$= \sum_{i=1}^{400} g[i]u[n-i]. \tag{13}$$

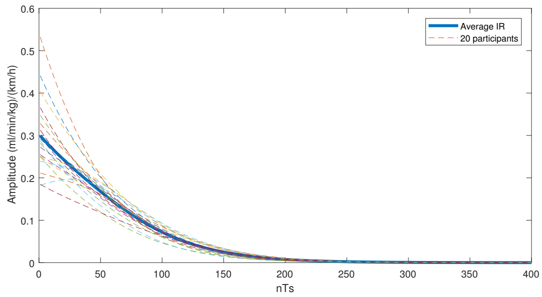

Fig. 7 Average IR and individual IR from 20 participants during the onset period of treadmill.

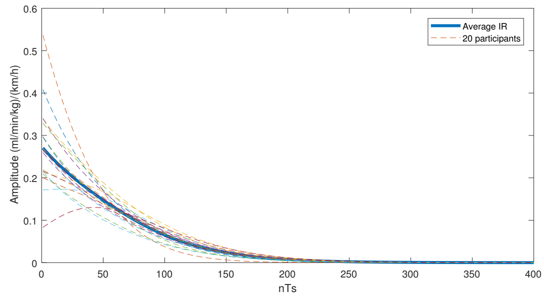

Fig. 9 Average IR and individual IR from 20 participants during the offset period of treadmill.

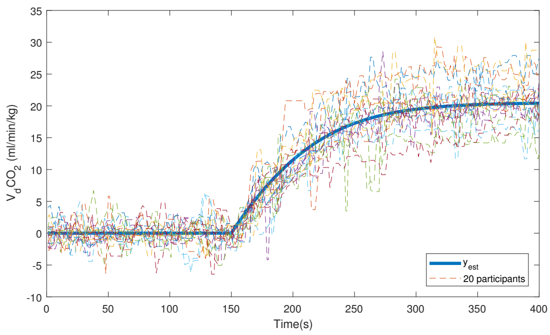

Fig. 8 Comparison between estimated V_dCO_2 and measurements from 20 participants during the onset period.

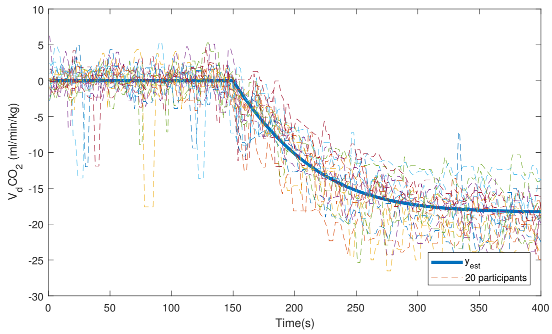

Fig. 10 Comparison between estimated V_dCO_2 and measurements from 20 participants during the offset period of the treadmill.

After the pre-processing, we apply the kernel based estimation method to estimate the IR model by using the SS kernel ($c = 1, \beta = 0.987, \gamma = 200$) as introduced in Section 2.

For the onset period of the treadmill exercise, the estimated impulse response of all participants (dotted line) and the average IR (bold line) are shown in Fig. 7. The response patterns are similar for most participants, but the individual differences do exist, which indicate that simply use of a first order model is not sufficient to describe the dynamic response of V_dCO_2. This is actually an advantage of adopting nonparametric modelling approach. The predicted V_dCO_2 output marked (bold line) are compared with the measured V_dCO_2 of each participant (dotted line) as shown in Fig. 8. It can be seen that the estimation fits well with the actual measurements regarding high goodness-of-fit.

3.3 Modelling of Offset Period

We select the data from t_1=901s to t_2=1300s for the modelling of offset period. Similar to the onset period, the original data are interpolated and filtered. The average value of the offset period for the initial 150 data is removed. The sampling time and the order of the impulse response model are selected as those of onset. The parameters of the kernel are also the same. The estimated impulse response of all participants (dotted line), as well as the, averaged IR (bold line) is shown in Fig. 9.

Again, most participants have a similar IR pattern, but some of them have a pattern which is quite different with the response of a first order system. The predicted V_dCO_2 output (bold line) and the actual V_dCO_2 of each participant (dotted line) are shown in Fig.10.

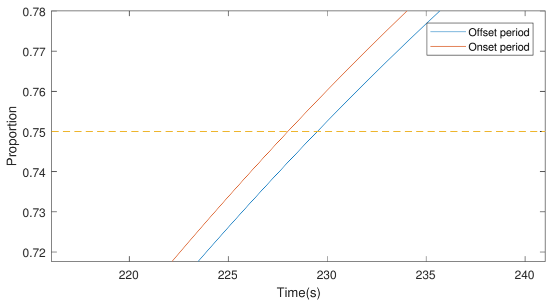

Fig. 11 The normalization of V_dCO_2 in onset and offset period (Partial magnification).

3.4 Comparison between Onset and Offset Period

To see this difference in the response speed, we normalized the averaged estimation of V_dCO_2 in onset and offset period, which is shown in Fig. 11.

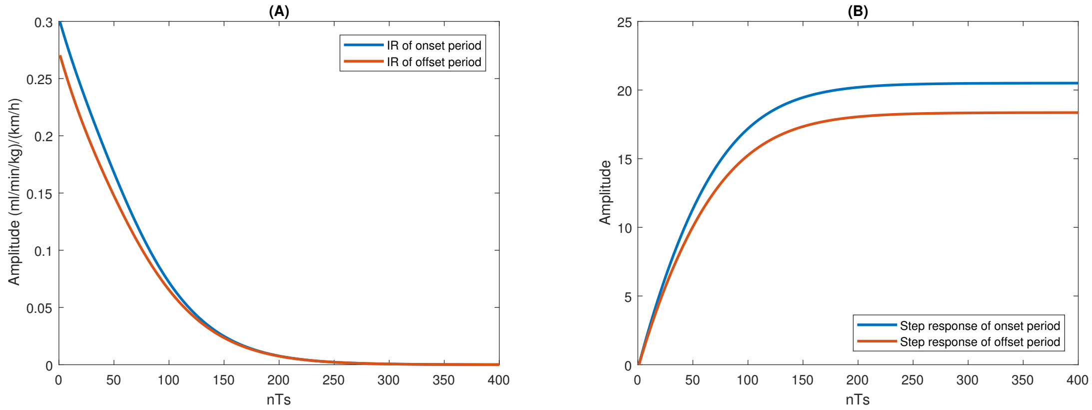

Fig. 12 Comparison between average IR and SR of V_dCO_2 in onset period and offset period.

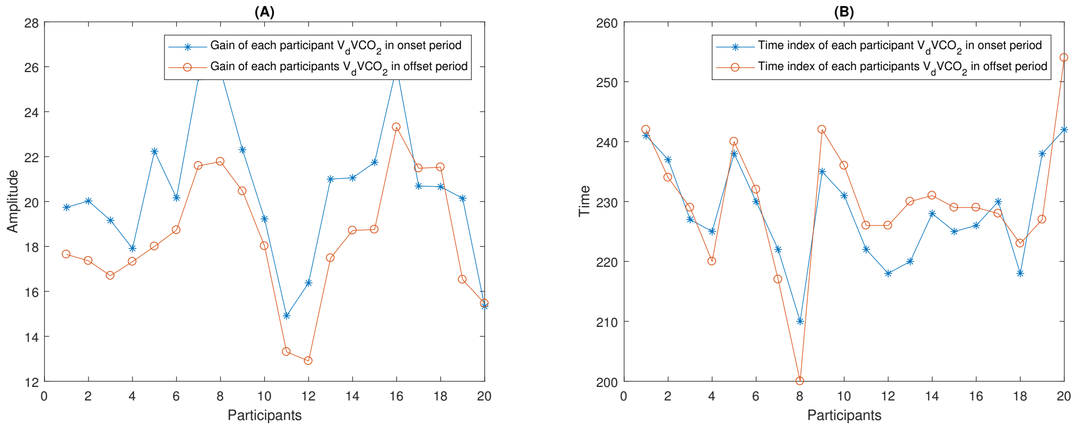

Fig. 13 The comparison of individual gain(A) and Time Index(B) of V_dCO_2 in onset and offset.

To show the transient behaviors, e.g., the response time, the Step Response (SR) of each participant and the averaged SR are plotted both in onset and offset period. From the comparison of the average IR and SR between onset and offset period in Fig. 12, we find that the gain of the onset period is bigger than that of the offset. Meanwhile, the response speed for the IR and SR of the two periods are slightly different.

For a thorough individual analysis, we plot the gain and "Time Index" of each participant which is shown in Fig. 13. The *histogram* and *normal probability* plotted in Matlab indicate that the individual Time Index follows the normal distribution while the individual gain does not strictly follow. Thus we applied *Paired T*-test for individual Time Index and test for individual gain using Matlab. The outcomes of the paired T-test and Ranks Sum test for Time index and Gain about V_dCO_2 in onset and offset are shown in Table 2.

According to the outcomes (i.e. Table 2), the Time Index of onset and offset shows no significant difference. Jerzy's research [26] reported a similar result about VO_2. For the steady-state gain, we can compare the mean value of 20 participants, 20.50 for onset and 18.35 for offset. Compared to the offset period, the higher gain in the onset period indicates a higher ratio between output and input. In other words, the results of our study show that for the same speed change, human body exhales out more CO_2 in the onset than offset. We will give a detail explanation in the next section. Hunt's research in Heart Rate (HR) modelling and control [28] also drew a similar conclusion for HR response.

Table 2 The statistic test outcome of V_dCO_2 in onset and offset

Item	Paired T-test	Rank sum test
Time Index	h=0, p=0.2539	–
Gain	–	h=1, p=0.0411

3.5 Comparison of V_dCO_2 and V_dO_2

Various comparisons, including IR, SR, and estimated output for V_dCO_2 and V_dO_2, for both onset period and offset period, are shown in Fig. 14 and Fig. 15, where clearly show that the changing of carbon dioxide is dynamically correlated to the changing of oxygen, during onset and offset exercise.

As the calculated correlation coefficient is 0.9991 in onset period and 0.9990 in offset period respectively, the high correlation between these two variables can be confirmed.

That means in some cases, the V_dO_2 can be approximately estimated by V_dCO_2, even in the transient period, or vice versa. This may be helpful to simplify the experimental procedure, as well as to reduce the cost of equipment maintenance. For example, for the gas collection during the experiment, it is often the case that the assessment of the exhaled gas components (with more carbon dioxide) is simpler than that of the inhaled gas (with more oxygen), i.e., the measurement of carbon dioxide production is more convenient than that of oxygen consumption. Then, if it is necessary, the measurement of V_dO_2 can be bypassed, but estimated by using V_dCO_2 instead to reduce the cost.

To show interpersonal differences, the gain and Time Index of each participant in onset and offset period are shown in Fig. 16 and Fig. 17. The histogram and normal probability of them are plotted in Matlab to decide which test methods will be applied.

Similar to the last subsection, we applied Paired T-test for individual Time Index and Rank Sum test for individual gain (using Matlab) according to whether they follow the normal distribution or not. The outcomes are shown in Table 3 and Table 4.

According to the above outcomes, the gain of V_dCO_2 and V_dO_2 in both periods shows no significant difference. Then for the Time Index of the two periods, we can compare the mean value of 20 participants, 228.15 for V_dCO_2 and 219.80 for V_dO_2 in onset; 229.75 for V_dCO_2 and 220.05 for V_dO_2 in offset. It indicates that the V_dO_2 shows a quicker response speed in both periods.

To further verify the conclusion, the difference of Time Index (V_dCO_2 minus V_dO_2) in two periods are calculated. As the differences are all positive, it further validated the conclusion.

Table 3 The statistic test outcome of V_dCO_2 and V_dO_2 in the onset

Item	Paired T-test	Rank Sum test
Time Index	h=1, p=6.96×10^{-6}	–
Gain	–	h=0, p=0.0720

Table 4 The statistic test outcome of V_dCO_2 and V_dO_2 in the offset

Item	Paired T-test	Rank Sum test
Time Index	h=1, p=6.54×10^{-6}	–
Gain	–	h=1, p=0.3942

4 Discussion

In this section, we attempt to explain the results from a physiological point of view. The explanation about the similarity and difference between onset vs. offset and V_dCO_2 vs. V_dO_2 are illustrated respectively in Subsection 4.1 and 4.2.

Aerobic respiration produces carbon dioxide and water, resulting in the releasing of energy and generating large amounts of Adenosine Triphosphate (ATP, also known as adenine nucleoside triphosphate). ATP transports chemical energy within cells for metabolism. Under normal circumstances, only considering the case of glucose for energy, in aerobic breathing, the product is carbon dioxide and water. The total reaction of aerobic respiration is shown in Eq. (14). The concept of Respiratory Quotient [31] (referred as RQ or R, the VCO_2 divided by VO_2 in local tissue) was presented, which is equal to 1 when glucose is the only available source for energy according to Eq. (14). Every one litre of oxygen will produce one litre of carbon dioxide and the volume ratio of carbon dioxide and oxygen is 1 [29][30]:

$$C_6H_{12}O_6 + 6O_2 + 6H_2O \xrightarrow{enzyme} 6CO_2 + 12H_2O + large\ amount\ of\ energy. \tag{14}$$

Based on the above background about aerobic respiration, the results and their physiological explanations are summarized as follows.

4.1 Comparison between Onset and Offset Period of V_dCO_2

– The Time Index of V_dCO_2 in onset is similar to offset and the gain of V_dCO_2 in onset is bigger than offset.

As we observed, for the same speed change, the carbon dioxide consumption in onset is more than offset. The reason behind this observation is the fact that ATP is the "molecular currency" for intracellular energy transfer, storage as well as transfer chemistry energy. With the increasing of the exercise intensity, the human body has to consume more ATP in onset period than that of in offset period. Human body provides ATP and produces carbon dioxide by respiration. Thus, the participants produce more carbon dioxide in onset period than offset for the same speed changing rate. This observation is also related to the "oxygen debt" [4][32][34], which is first proposed by Hill [3]. The "debt" occurs during the onset period because the stored credits are expended.

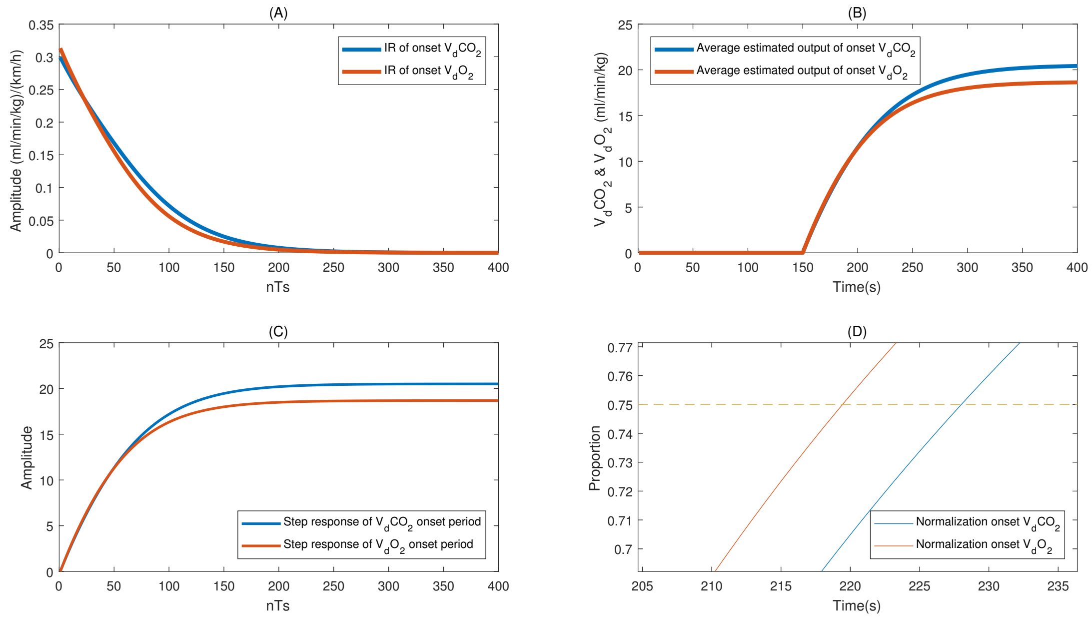

Fig. 14 (A)Comparison between average IR of V_dCO_2 and V_dO_2 during onset period. (B)Comparison between average estimation output of V_dCO_2 and V_dO_2 during onset period. (C)Comparison between average SR of V_dCO_2 and V_dO_2 during onset period. (D)The normalization of estimated V_dCO_2 and V_dO_2 in onset period (Partial magnification).

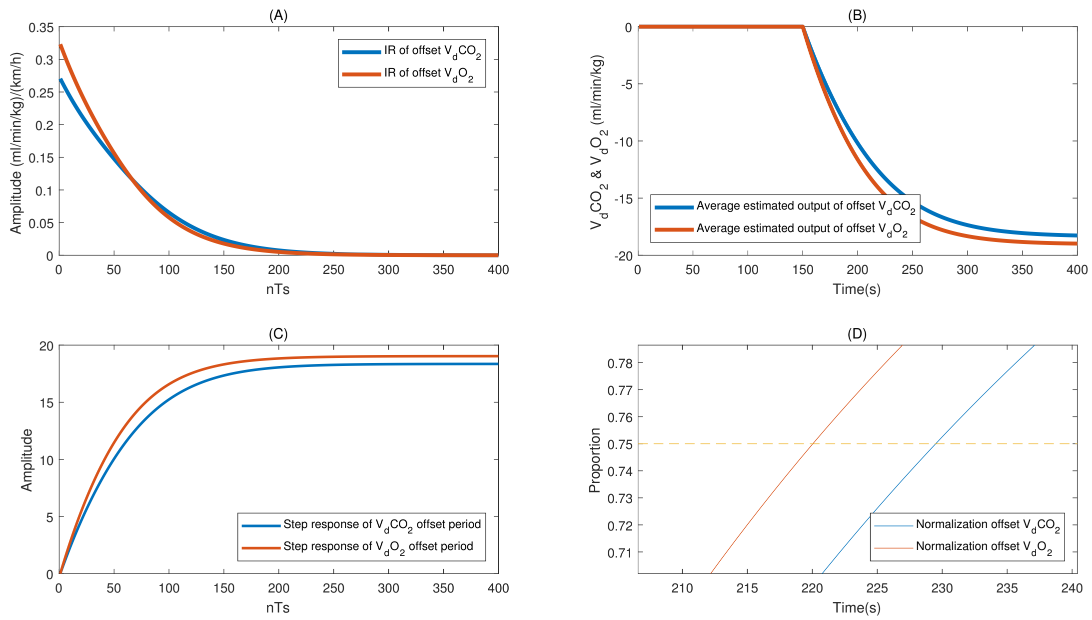

Fig. 15 (A)Comparison between average IR of V_dCO_2 and V_dO_2 during offset period. (B)Comparison between average estimation output of V_dCO_2 and V_dO_2 during offset period. (C)Comparison between average SR of V_dCO_2 and V_dO_2 during offset period. (D)The normalization of estimated V_dCO_2 and V_dO_2 in offset period (Partial magnification).

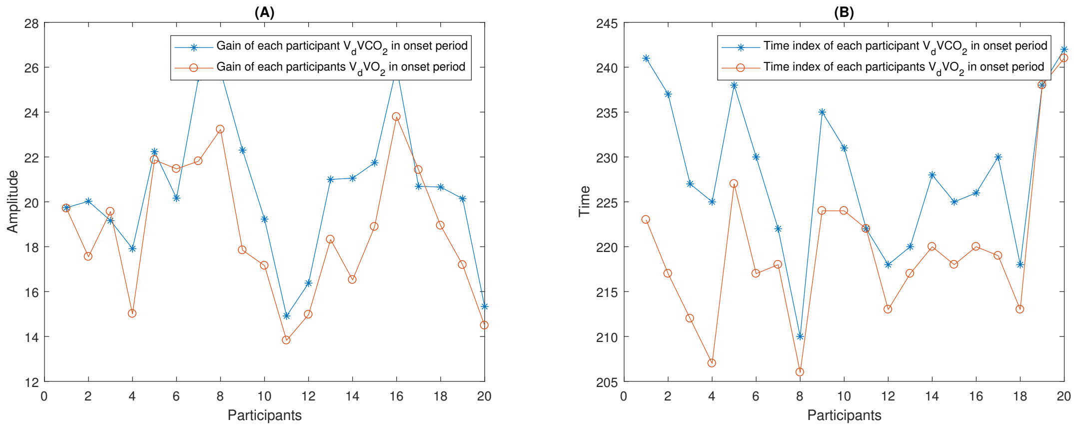

Fig. 16 The comparison of individual gain (A) and Time Index (B) between V_dCO_2 and V_dO_2 in onset.

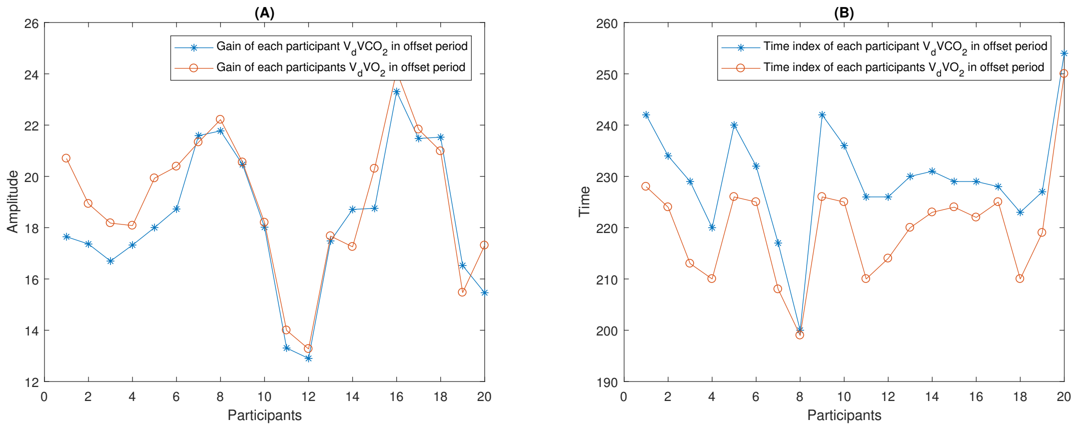

Fig. 17 The comparison of individual gain (A) and Time Index (B) between V_dCO_2 and V_dO_2 in offset .

4.2 Comparison of V_dCO_2 and V_dO_2

– Similarity: The V_dCO_2 and V_dO_2 are significantly related, and the gains of V_dCO_2 and V_dO_2 are similar in both periods.

The similar gain and correlation coefficient of V_dCO_2 and V_dO_2 also work in concert with the respiration formula as Eq. (14).

– Difference: The Time Index of V_dCO_2 is bigger than that of V_dO_2 in both periods, so the V_dO_2 shows a quicker response speed.

The different Time Index means a different gas delivery rate. The Fig. 3 in Williams's research [33] shows the same result. For their half-time constant, oxygen consumption is smaller than carbon dioxide elimination. This is also related to the O_2 debt and excess CO_2 and respond to the Subsection 4.1. The Fig. 2 of Karlman's research [4] also shows that the R is over 1 which is same to our results and explain it by a buffer system.

5 Conclusion

This study investigates the onset and offset dynamics of cardiorespiratory response to treadmill exercise. In order to detect the characteristic differences during onset and offset exercise, a recently developed nonparametric modelling method based on l^2-norm kernel regularization has been applied to identify the impulse responses of the carbon dioxide production (V_dCO_2) and oxygen consumption (V_dO_2) responses. By well-designed kernel based regularization term, this approach can handle the data with short records and low SNR (Signal-to-Noise-Ratio), and orderly fit the experimental data. In terms of the fitness for the experimental data from twenty healthy subjects, the stable spline (SS) kernel achieves a reliable estimation of the impulse response for both V_dCO_2 and V_dO_2. Based on the identified impulse response model, various statistical comparisons are developed and the comparison results are explained from physiological perspective. The bigger gain of V_dCO_2 in onset demonstrates the human's ATP storage during the relaxing status. Meanwhile, the quicker response speed of V_dCO_2 in both periods explains why there is a delay due to the conversion from O_2 to CO_2. We believe the kernel based nonparametric modelling approach together with the developed impulse response models will significantly improve our understanding of human cardiorespiratory response to exercise, and provide instructive guidance for the regulation of exercise intensity to ensure the efficiency and safety during training and rehabilitation exercises.

References

1. McLaughlin JE, King GA, Howley ET, Bassett Jr DR, Ainsworth BE. Validation of the cosmed k4b2 portable metabolic system. *International journal of sports medicine*, 22(04):280–284, 2001.
2. Henning B, Löfgren R, and Sjöström L. Chamber for indirect calorimetry with improved transient response. *Medical and Biological Engineering and Computing*, 34(3):207–212, 1996.
3. Archibald V Hill, CNH Long, and H Lupton. Muscular exercise, lactic acid, and the supply and utilisation of oxygen. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character*, 97(681):84–138, 1924.
4. Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. *J appl Physiol*, 35(82):236, 1973.
5. Mukhopadhyay S, Sircar P. . Parametric modelling of ECG signal. *Medical and Biological Engineering and computing*, 34(2):171–174, 1996.
6. Lu L, Hamzaoui L, Brown BH, Rigaud B, Smallwood RH, Barber DC, Morucci JP. Parametric modelling for electrical impedance spectroscopy system. *Medical and Biological Engineering and Computing*, 34(2):122–126, 1996.
7. Lin CC, Chen CM, Yang IF, Yang TF. Automatic optimum order selection of parametric modelling for the evaluation of abnormal intra-qrs signals in signal-averaged electrocardiograms. *Medical and Biological Engineering and Computing*, 43(2):218–224, 2005.
8. Steven W Su, Lu Wang, Branko G Celler, and Andrey V Savkin. Oxygen uptake estimation in humans during exercise using a Hammerstein model. *Annals of biomedical engineering*, 35(11):1898–1906, 2007.
9. Steven W Su, Lu Wang, Branko G Celler, Andrey V Savkin, and Ying Guo. Identification and control for heart rate regulation during treadmill exercise. *IEEE Transactions on biomedical engineering*, 54(7):1238–1246, 2007.
10. Steven W Su, Lu Wang, Branko G Celler, Andrey V Savkin, and Ying Guo. Modelling and control for heart rate regulation during treadmill exercise. In *Engineering in Medicine and Biology Society, 2006. EMBS'06. 28th Annual International Conference of the IEEE*, pages 4299–4302. IEEE, 2006.
11. Tianshi Chen, Henrik Ohlsson, and Lennart Ljung. On the estimation of transfer functions, regularizations and gaussian processesrevisited. *Automatica*, 48(8):1525–1535, 2012.
12. Gianluigi Pillonetto, Alessandro Chiuso, and Giuseppe De Nicolao. Prediction error identification of linear systems: a nonparametric gaussian regression approach. *Automatica*, 47(2):291–305, 2011.
13. Gianluigi Pillonetto and Giuseppe De Nicolao. A new kernel-based approach for linear system identification. *Automatica*, 46(1):81–93, 2010.
14. Hannes Leeb and Benedikt M Pötscher. Model selection and inference: Facts and fiction. *Econometric Theory*, 21(1):21–59, 2005.
15. Tianshi Chen, Martin S Andersen, Lennart Ljung, Alessandro Chiuso, and Gianluigi Pillonetto. System identification via sparse multiple kernel-based regularization using sequential convex optimization techniques. *IEEE Transactions on Automatic Control*, 59(11):2933–2945, 2014.
16. Tianshi Chen and Lennart Ljung. Implementation of algorithms for tuning parameters in regularized least squares problems in system identification. *Automatica*, 49(7):2213–2220, 2013.
17. Gianluigi Pillonetto and Giuseppe De Nicolao. Kernel selection in linear system identification part i: A gaussian process perspective. In *Decision and Control and European Control Conference (CDC-ECC), 2011 50th IEEE Conference on*, pages 4318–4325. IEEE, 2011.
18. Gianluigi Pillonetto, Francesco Dinuzzo, Tianshi Chen, Giuseppe De Nicolao, and Lennart Ljung. Kernel methods in system identification, machine learning and function estimation: A survey. *Automatica*, 50(3):657–682, 2014.
19. Alessandro Chiuso, Tianshi Chen, Lennart Ljung, and Gianluigi Pillonetto. Regularization strategies for nonparametric system identification. In *Decision and Control (CDC), 2013 IEEE 52nd Annual Conference on*, pages 6013–6018. IEEE, 2013.
20. Tianshi Chen and Lennart Ljung. On kernel design for regularized LTI system identification. *arXiv preprint arXiv:1612.03542*, 2016.
21. Tianshi Chen, Henrik Ohlsson, Graham C Goodwin, and Lennart Ljung. Kernel selection in linear system identification part ii: A classical perspective. In *Decision and Control and European Control Conference (CDC-ECC), 2011 50th IEEE Conference on*, pages 4326–4331. IEEE, 2011.
22. American College of Sports Medicine. *Guidelines for exercise testing and prescription*. Williams & Wilkins, 1991.
23. Van der Walt WH, Wyndham CH. An equation for prediction of energy expenditure of walking and running. *Journal of Applied Physiology*, 34(5):559–563, 1973.
24. Daijiro Abe, Kazumasa Yanagawa, and Shigemitsu Niihata. Effects of load carriage, load position, and walking speed on energy cost of walking. *Applied ergonomics*, 35(4):329–335, 2004.
25. L Puente-Maestu, ML Sanz, P Sanz, JM Ruiz De Ona, JL Rodriguez-Hermosa, and BJ Whipp. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *European Respiratory Journal*, 15(6):1026–1032, 2000.
26. Jerzy A Zoladz, Bruno Grassi, Joanna Majerczak, Zbigniew Szkutnik, Michal Korostyński, Marcin Grandys, Wieslawa Jarmuszkiewicz, and Bernard Korzeniewski. Mechanisms responsible for the acceleration of pulmonary VO2 on-kinetics in humans after prolonged endurance training. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 307(9):R1101–R1114, 2014.
27. Polle DC, Jones AM. Towards an understanding of the mechanistic bases of VO2 kinetics: summary of key points raised in chapters 211. *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*, pages 294–328, 2007.
28. Kenneth J Hunt, Simon E Fankhauser, and Jittima Saengsuwan. Identification of heart rate dynamics during moderate-to-vigorous treadmill exercise. *Biomedical engineering online*, 14(1):117, 2015.
29. PR Rich. The molecular machinery of Keilin's respiratory chain, 2003.
30. Lubert Stryer. Biochemistry, 1995. *Newyork, NY: WH Freeman and Co, Fourth Google Scholar*, 1995.
31. François Peronnet, Denis Massicotte, et al. Table of nonprotein respiratory quotient: an update. *Can J Sport Sci*, 16(1):23–29, 1991.
32. Yi Zhang, Azzam Haddad, Steven W Su, Branko G Celler, Aaron J Coutts, Rob Duffield, Cheyne E Donges, and Hung T Nguyen. An

equivalent circuit model for onset and offset exercise response. *Biomedical engineering online*, 13(1):145, 2014.

33. William E Berg. Individual differences in respiratory gas exchange during recovery from moderate exercise. *American Journal of Physiology–Legacy Content*, 149(3):597–610, 1947.
34. Nicholas M Beltz, Fabiano T Amorim, Ann L Gibson, Jeffrey M Janot, Len Kravitz, Christine M Mermier, Nathan Cole, Terence A Moriarty, Tony P Nunez, Sam Trigg, et al. Hemodynamic and metabolic responses to self-paced and ramp-graded exercise testing protocols. *Applied Physiology, Nutrition, and Metabolism*, (999):1–8, 2018.

Response letter

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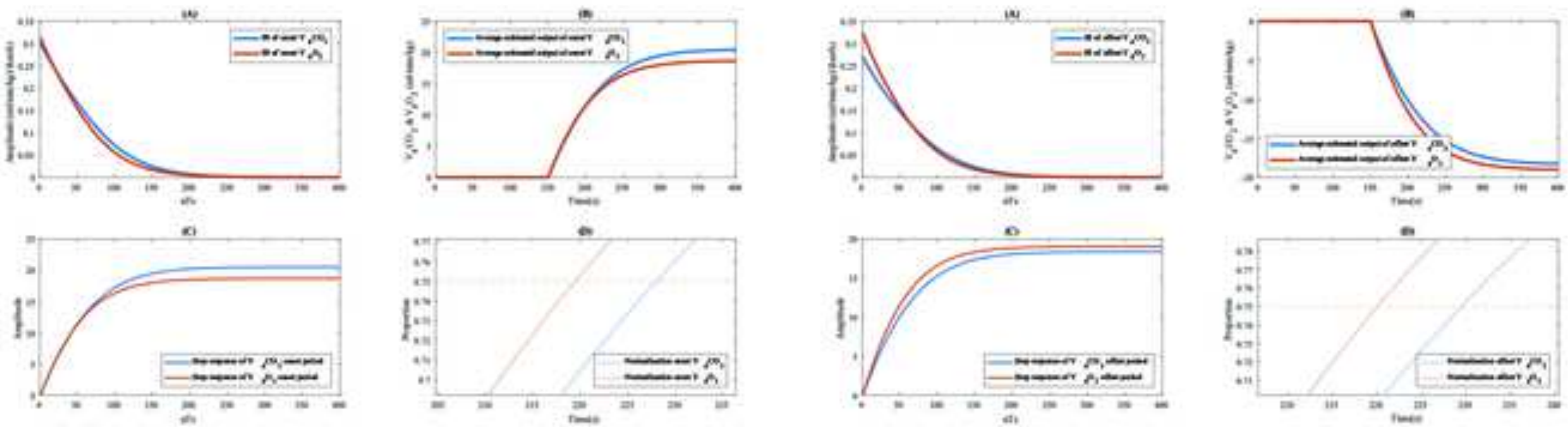

(A)Comparison between average IR of and during onset and offset period.

(C)Comparison between average SR of and during onset and offset period.

(B)Comparison between average estimation output of and during onset and offset period.

(D)The normalization of estimated and in onset and offset period (Partial magnification).